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REMARKS

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

Claims 1, 3, and 26 to 28 were acted upon by the Examiner in the Office Action dated November 17, 2003. No claims are withdrawn. Claims 1, 3, and 26 to 28 have been amended. No claims have been canceled. No claims have been added. Accordingly, Claims 1, 3, and 26 to 28 are presented for examination.

Support for Amendment to Claims 26 to 28

The amendments to Claims 1 and 3 are editorial in nature and as such do not constitute the addition of new matter. Support for the amendments to Claims 26 to 28 is found on page 2, line 27, to page 3, line 10, and on page 4, line 23, to page 5, line 6.

ARGUMENTS

In response to the Examiner's Office Action dated November 17, 2003, Applicants respectfully traverse the Examiner's rejection of Claims 1, 3, and 26 to 28.

The §102(a) Rejections

The Rejection of Claims 1 and 3

The Examiner has rejected Claims 1 and 3 under 35 U.S.C. §102(a) as being anticipated by Sugano et al., Online EMBL Database; "Homo sapiens cDNA FLJ20177 fis, clone COL09966, highly similar to Y08136 H", Accession No.: AK000184.

Applicant respectfully traverses the rejection.

MPEP §715 states (emphasis added):

> Affidavits or declarations under 37 CFR 1.131 may be used, for example:
>
> (A) To antedate a reference or activity that qualifies as prior art under 35 U.S.C. 102(a) and not under 35 U.S.C. 102(b), e.g., where the prior art date under 35 U.S.C. 102(a) of the patent, the publication or activity used to reject the claim(s) is less than 1 year prior to applicant's or patent owner's effective filing date.

Accordingly, Applicants submit herewith a declaration under 37 CFR §1.131, dated April 9, 2004 and signed by inventor June Kaplow on April 13, 2004, which establishes the invention of SEQ ID NO:3 by Applicants prior to the publication of Sugano et al. The declaration makes reference to a Record of Invention (ROI), with

dates redacted, prepared by inventor June Kaplow prior to February 15, 2000. A copy of this ROI has been provided.

Page 1, Section 2 of the ROI refers to "The nucleotide sequence of clone 7a, clone 14b" which is included as an attachment to the ROI (pages 9 and 10). The nucleotide sequence of clone 14b is the same as SEQ ID NO:3 of the present application.

Exhibit B is a sequence comparison of clone 14b/SEQ ID NO:3 and the sequence disclosed in Sugano et al. Applicants concur with the Examiner's assertion that clone 14b/SEQ ID NO:3 and the sequence disclosed in Sugano et al. comprise 1361 out of 1362 identical residues (nucleotide 481 of clone 14b/SEQ ID NO:3 is different that nucleotide 553 of the sequence disclosed in Sugano et al.).

The declaration and supporting documents establish that the date of invention for clone 14b/SEQ ID NO:3 by Applicants was prior to the publication of Sugano et al. Accordingly, applicants respectfully request withdrawal of the rejections of Claims 1 and 3 under 35 U.S.C. §102(a) as being anticipated by Sugano et al.

The §101 Rejections

The Rejection of Claims 1 and 26 to 28

The Examiner has rejected Claim 1 under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. In particular, Claim 1 recites, "A nucleic acid...".

Applicants have amended Claim 1 to recite, "An isolated nucleic acid...". In view of this amendment, Applicants respectfully request withdrawal of the rejections to Claim 1 under 35 U.S.C. §101.

The Examiner has rejected Claims 26 to 28 under 35 U.S.C. §101 because the claimed recitation of a use results in an improper definition of a process.

Applicants have amended Claims 26 to 28 to recite methods for "treatment or prevention of an NFκB-regulated inflammatory response in a patient comprising administering to said patient" nucleic acids and vectors of the present invention. Accordingly, Claims 26 to 28 now recite a process comprising the step of "administering". In view of these amendments, Applicants respectfully request withdrawal of the rejections to Claims 26 to 28 under 35 U.S.C. §101.

The §112, second paragraph, Rejections

The Rejection of Claims 3 and 26 to 28

The Examiner has rejected Claim 3 under 35 U.S.C. §112, second paragraph, for failing to particularly pont out and distinctly claim the invention. In particular, the phrase "said DNA" of Claim 3, which depends from Claim 1, lacks antecedent basis.

Applicants have amended Claim 3 to recite, "The nucleic acid of Claim 1 wherein said nucleic acid is a cDNA.". Accordingly, Claim 3 now no longer lacks antecedent basis. In view of this amendment, Applicants respectfully request withdrawal of the rejections to Claim 3 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected Claims 26 to 28 under 35 U.S.C. §112, second paragraph, because the claimed recitation of a use does not set forth any steps involved in the process.

Applicants have amended Claims 26 to 28 to recite methods for "treatment or prevention of an NFκB-regulated inflammatory response in a patient comprising administering to said patient" nucleic acids and vectors of the present invention. Accordingly, Claims 26 to 28 now all comprise the step of "administering". In view of these amendments, Applicants respectfully request withdrawal of the rejections to Claims 26 to 28 under 35 U.S.C. §112, second paragraph.

A favorable action on the merits is requested respectfully. A Petition for a two-month extension of time to respond to the Action, from February 17, 2004 to

April 17, 2004, a Saturday, is enclosed.

Respectfully submitted,

Jonathan M. Dermott, Ph.D.
Registration No. 48,608

SYNNESTVEDT & LECHNER LLP
Suite 2600 Aramark Tower
1101 Market Street
Philadelphia, Pennsylvania 19107
(215) 923-4466

M:\JDermott\Aventis Pharma\23,461-A USA\reply to oa dated 2003.11.17.wpd

April 9, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re/ Application of June Kaplow,
Thomas Haws, Marie Rosier,
and Patrice Denefle
Application No. 09/823,119
Filed March 30, 2001

Examiner: J.L. Epps-Ford, Ph.D.
Art Unit: 1635
Confirmation No. 9257

NUCLEAR FACTOR KB
INDUCING FACTOR

Attorney Docket No. P23,461-A USA

DECLARATION UNDER 37 CFR §1.131

Sir:

I, June Kaplow, hereby declare as follows:

1. I am a United States citizen. I was an employee of Rhone-Poulenc Rorer Inc. (now known as Aventis Pharmaceuticals Inc.), working in the United States prior to and during the discovery of the present invention claimed in U.S. Patent Application No. 09/823,119..

2. I am an inventor of the subject matter claimed in the above-identified patent

application.

3. I am aware that Sugano et al., Online EMBL Database; "Homo sapiens cDNA FLJ20177 fis, clone COL09966, highly similar to Y08136 H", Accession No.: AK000184, has been cited as prior art by the Examiner in the Office Action, dated November 17, 2003, with respect to Claims 1 and 3 of the above-identified application. Sugano et al. was submitted to GenBank on February 15, 2000.

4. This declaration is to establish completion of the invention in the above-identified application in the United States at a date prior to February 15, 2000.

5. Prior to February 15, 2000, I completed my invention as described and claimed in the subject application in this country, as more particularly detailed below:

a. Prior to February 15, 2000, having earlier conceived of the subject matter now being claimed, I prepared a Record of Invention (ROI) form entitled "The cloning and characterization of two alternatively spliced genes encoding human 'acid' sphingomyelinase phosphodiesterase 3a herein referred to as clone 7a (short) and clone 14b (long)". The ROI included a detailed description of the invention now being claimed in the above-identified patent application, including the nucleotide sequence of clone 14b (see Section 2 of ROI). I submitted the form to the Patent Department. The Patent Department assigned a file number and date-stamped the submission form prior to February 15, 2000. A copy of the ROI and associated documents listed in Section 2 of the ROI, with the dates redacted, are attached hereto as Exhibit A.

b. Exhibit A provides details of the features and elements of the claimed invention. More specifically, they describe a nucleotide sequence disclosed in the presently claimed application as "NFIF 14b" or SEQ ID NO:3 (see also Figure 3). Of the 1362 nucleotides of SEQ ID NO:3, 1361 are identical to nucleotides 72-1433 of Sugano et al. Exhibit B shows an alignment between these two nucleic acids.

6. As the person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Inventor: June Kaplow

Signature: June Kaplow 4/13/04
Date

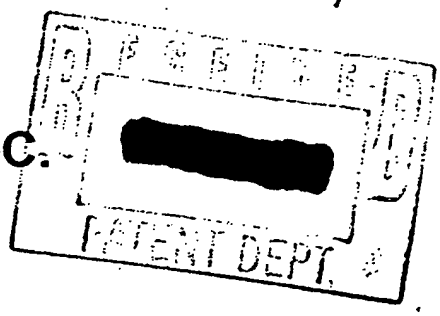
Residence: Doylestown, PA

Citizenship: USA

Exhibit A

43539

Computer Entered



RHÔNE-POULENC RORER INC.

RECORD OF INVENTION

[ORIGINAL TO BE RETAINED BY PATENT DEPT.]

DATE [redacted]

1. **SHORT TITLE OF DEVELOPMENT:**

The cloning and characterization of two novel alternatively spliced genes encoding human 'acid' sphingomyelinase phosphodiesterase 3a herein referred to as clone 7a (short) and clone 14b (long).

2. **GENERAL DESCRIPTION:** (If new chemical compounds - general formula and preparation from known starting materials, and RPR Nos. & Formulas of all compounds prepared. If pharmaceutical composition - ingredients, proportions and preparations. If machine or process - critical components and operation. Attach additional pages or diagrams if necessary. Best mode of preparation and/or use should be included.)

Two human clones encoding acid sphingomyelinase phosphodiesterase 3a gene (ASMPD3a) have been PCR cloned from placenta and brain cDNA libraries. The clones were transfected into mammalian cell lines to establish a permanent cell line.

Included: Comparison of the amino acid sequence of the two variants versus the known smpd1 and mouse asmpd3a.

The transcripts identified in the bioinformatics search.

The nucleotide sequence of clone 7a, clone 14b.

The amino acid sequence of the brain isoforms (transcript E) identified by bioinformatics analysis and wet bench.

3. **UTILITY:** (Point out the use of invention. Indicate specific compounds of interest by name and RPR number with key test results.)

a. We have demonstrated that the porcine and mouse mRNA encoding asmpd3a was respectively upregulated in coronary arteries isolated from porcine (high cholesterol, high fat diet, or diet plus balloon angioplasty) and mouse (apo E K/0- Western diet) animal models of atherosclerosis. Thus the human gene counterpart may be a novel target for therapeutic intervention in the treatment of coronary artery or associative inflammatory diseases. The stable overexpressing cell line may be useful to screen for antagonists. No function has been reported with the previously cloned mouse asmpd3a gene.

b. Our demonstration of sphingomyelin as the substrate for asmpd3a suggests that asmpd3a overexpression in atherosclerosis may enhance foam cell formation. LDL-SM is highly enriched in atherosclerotic lesions and hydrolysis of LDL-SM promotes the retention, subendothelial aggregration and eventual uptake of LDL by macrophage [shown by Schissel et al. for asm-1 (SMPD1)]. Therefore the presence of this enzyme in the arterial wall may be detrimental to the progression of atherosclerosis.

c. We have also shown that the mRNA for asmpd3a is upregulated in rat models of ischemia (apoptosis). Apoptosis has been demonstrated in atherosclerotic coronary arteries and is localized in macrophage, smooth muscle cell and endothelial cells. Apoptotic events may cause foam cell death thus accelerating plaque progression. Additionally it has been shown that apoptosis of macrophages/Tcells may shed membrane microparticles that retain procoagulant potential (Ziad Mallat et al. Circulation 1999). Thus the activation of asmpd3a may play a role in plaque thrombogenicity. Thrombogenic related episodes are the leading cause of coronary death associated with atherosclerosis.

d. The gene itself may be useful as a gene therapy agent if there are mutations identified that delete its activity.

4. **NOVELTY:** (Describe how your invention differs from what is in the public domain or differs from what you are aware was done before).

The mouse gene for acid sphingomyelinase phosphodiesterase 3a has been previously cloned and the sequence deposited in the public domain. We examined diseased versus normal differentially expressed genes using suppressive subtractive hybridization technology applied to RNA extracted from coronary arteries of pigs. These pigs underwent a balloon angioplasty which was superimposed over a high fat high cholesterol diet and we have identified through sequence analysis, a 3' fragment of the pig homolog to the mouse asmpd3a gene. There is no previous information on the pig isoform of asmpd3a. Since we are interested in pharmaceuticals directed toward human coronary events, the cloning of the human counterpart of asmpd3a would be required. Up to the time we initiated this project and to the present there still is no literature characterizing the mouse asmpd3a gene nor has the human gene been cloned. Given the 3' pig sequence which aligned 99% to the human 3' sequence that is available in the public domain, and given this genes' apparent upregulation in this disease state, we attempted to use anchored PCR and walk up the sequence. This only extended the clone another 100 bp. All attempts at degenerate PCR using oligonucleotides designed off the full length mouse sequence were not successful. Therefore we used a bioinformatics approach to find clusters that overlapped the known sequence and extended the sequence 5' in silico. The translation of this sequence did not result in a full length open reading frame. We went back and designed PCR primers to what appeared to be an ATG start codon and hoped this partial virtual sequence information would be correct. The sequence we obtained retained similarity to the bioinformatics clustal alignment but then diverged and downstream picked up the already known 3' sequence. Sequencing of several PCR clones demonstrated more than one extended open reading frame. When aligned these two sequences appeared to be spliced variants of the human asmpd3a with an alignment to the mouse form at 79%. Additonally 3 other splice variants were isolated that did not yield ORFs. Since normal PCR, degenerative PCR and bioinformatics clustal overlap analysis did not result in the full length clone, we feel our approach was not obvious. Additionally, the information that was produced from Northern blot analysis gave us association that these clones are upregulated in the porcine and mouse models of atherosclerosis. The known active SMPD1 gene has 21% homology to the protein from our cloned gene candidates. SPDM1 is also alternatively spliced with 3 variants of which only one is an active enzyme.

5. **PROBLEM SOLVED:** (Describe the problem that may have been solved by your invention.)

The full length cloning of human asmpd3a and variants.

6. **WORKABLE EXTENT:** (Future course of related work. Possible variables of present invention.)

Depending on the regulation of the gene one or both forms may be important targets for coronary artery disease /ischemia due to the upcoming role of sphingomyelinases in apoptosis.

7. **RELATED LITERATURE:** (Include literature & patent references or RPR literature reviews on the compounds and analogs. Attach separate sheet if necessary.

Sphingolipids in Atherosclerosis and Vascular Biology Subroto Chatterjee Arterioscler Thromb Vasc. Biol 1998; 18:1523-1533.

Marathe S, et al. JBC Vol. 273 p4081-4088 1998 Human Vascular Endothelial Cells are a rich and regulatable source of secretory sphingomyelinase.SMPD1

Schissel S. et al. JBC Vol. 271 p18431-18436 1996 Zn+2 stimulated sphingomyelinase is secreted by many cell types and is a product of acid sphingomyelinase gene. SMPD1

Schuchman E. H. Et al. JBC Vol. 266 p8531-8539 1991 Human Acid Sphingomyelinase; Isolation, Nucleotide Sequence and Expression of the Full Length and Alternatively Spliced cDNAs (SMPD1)
Oorni K. Et al JBC Vol. 273 p29127-29134 1998 Sphingomyelinase induces aggregation and fusion but phospholipase A2 only aggregation, of low density lipoprotein LDL particles.: Two distinct mechanisms leading to increased binding strength of LDL to human aortic proteoglycans.

Submission of mouse asmpd3a- full length and human asmpd3a 838bp partial coding : Date 17 sept 1996, K. Hofmann, Isrec (Swiss Inst. F. Exp. Canc. Res.) Bioinformatics Group, Chemin des boveresses 155, Ch/1066 Epalinges S/ Lausanne Switzerland acc Y08135 Y08136

Tabas I. Et al Lipoprotein lipase and sphingomyelinase synergistically enhance the association of atherogenic lipoproteins with smooth muscle cells and extracellular matrix. A possible mechanism for low density lipoprotein and lipoprotein (a) retention and macrophage foam cell formation. JBC 1993 Vol. 268: 20419-20432

Mallat Z. Et al Shed Membrane Microparticles with procoagulant potential in human atherosclerotic plaques: a role for apoptosis in plaque thrombogencity Circulation 1999:99:348-353.

8. DATES OF:

a) Conception, on or before _____, by June Kaplow _____7379 p 91_____ reference_____

b) Written record _____, reference/notebook #_____

c) Disclosure_____ 19___, names_june kaplow.....

d) Started first prep._____ 19___, by _____ reference _____

APPROVAL FOR FILING:
(read and understood by)

1. Dept. Head (full name)
Bruce Miller
[redacted]

Full date: [redacted]

2. Senior Director
MARK PERRONE
[redacted]

Full date: _____

3. Div. Head

_____

Full date: _____

4. Patent Dept. Rep. Keith Baker
[redacted]

Full date: [redacted]

POSSIBLE INVENTOR(S): (Type or print names)

June Kaplow/ Bruce Miller

Tom Haws

Navin Jariwala

Asher Zilberstein

Ed Murray

Marie Rosier

Patrice Denefle

Are all inventors employed by RPR? Yes_X___ No_____

If not, affiliation of other inventors:

Submitted by: June Kaplow

Typed by: _____

Date: [redacted]

```
                MALVRAL----------------------------------------  Majority
                        10        20        30        40
1               MALVRAL----------------------------------------  HASM14BP.PRO
1               MALVRAL----------------------------------------  HASM7AP.PRO
1               MGLALALALALALSDSRVLWAPAEAHPLSPQGHPARLH  HASMSPD1.PRO
1               MALLGNF----------------------------------------  MASMPD.PRO

                ----------------------VC----------------------  Majority
                        50        60        70        80
8               ----------------------VC----------------------  HASM14BP.PRO
8               ----------------------VC----------------------  HASM7AP.PRO
41  RIVPRLRDVFGWGNLTCPICKGLFTAINLGLKKEPNVARV  HASMSPD1.PRO
8               ----------------------LC----------------------  MASMPD.PRO

                -------C----------------------------LLTAWH-----  Majority
                        90       100       110       120
10              -------C----------------------------LLTAWH-----  HASM14BP.PRO
10              -------C----------------------------LLTAWH-----  HASM7AP.PRO
81  GSVAIKLCNLLKIAPPAVCQSIVHLFEDDMVEVWRRSVLS  HASMSPD1.PRO
10              -------C----------------------------LLVAWL-----  MASMPD.PRO

                ----CGSGLG----------------LPVAPAGGRNPPPA-  Majority
                       130       140       150       160
17              ----CRSGLG----------------LPVAPAGGRNPPPA-  HASM14BP.PRO
17              ----CRSGLG----------------LPVAPAGGRNPPPA-  HASM7AP.PRO
121 PSEACGLLLGSTCGHWDIFSSWNISLPTVPKPPPKPPSPP  HASMSPD1.PRO
17              ----CGPGLG----------------VPLAPA---DRAPA-  MASMPD.PRO

                -----VGQFWHVTDLHLDPTYHITDDHT---KVCASSKGA  Majority
                       170       180       190       200
37              -----IGQFWHVTDLHLDPTYHITDDHT---KVCASSKGA  HASM14BP.PRO
37              -----IGQFWHVTDLHLDPTYHITDDHT---KVCASSKGA  HASM7AP.PRO
161 APGAPVSRILFLTDLHWDHDYLEGTDPDCADPLCCRRGSG  HASMSPD1.PRO
34              -----VGQFWHVTDLHLDPTYHITDDRT---KVCASSKGA  MASMPD.PRO

                NASNPGPFGDVLCD-SPYQLILSAFD-FIKNSGQEASF--  Majority
                       210       220       230       240
69              NASNPGPFGDVLCD-SPYQLILSAFD-FIKNSGQEASF--  HASM14BP.PRO
69              NASNPGPFGDVLCD-SPYQLILSAFD-FIKNSGQEASF--  HASM7AP.PRO
201 LPPASRPGAGYWGEYSKCDLPLRTLESLLSGLGPAGPFDM  HASMSPD1.PRO
66              NASNPGPFGDVLCD-SPYQLILSAFD-FIKNSGQEASF--  MASMPD.PRO

                MIWTGDSPPHVPVPELSTDTVINVITNMTTTVQSLFPNLQ  Majority
                       250       260       270       280
105             MIWTGDSPPHVPVPELSTDTVINVITNMTTTIQSLFPNLQ  HASM14BP.PRO
105             MIWTGDSPPHVPVPELSTDTVINVITNMTTTIQSLFPNLQ  HASM7AP.PRO
241 VYWTGDIPAH-DVWHQTRQDQLRALTTVTALVRKFLGPVP  HASMSPD1.PRO
102             MIWTGDSPPHVPVPELSTGTVIKVITNMTMTVQNLFPNLQ  MASMPD.PRO
```

[redacted]

```
    V F P A L G N H D Y W P Q D Q L P X V - - - - - - - T S K V Y X A V A X L W K P Majority
                      290                 300                 310                 320
145 V F P A L G N H D Y W P Q D Q L S V V - - - - - - - T S K V Y N A V A N L W K P HASM14BP.PRO
145 V F P A L G N H D Y W P Q - - - - - - - - - - - - - - - - - - - - - - - - - - - HASM7AP.PRO
280 V Y P A V G N H E S T P V N S F P P P F I E G N H S S R W L Y E A M A K A W E P HASMSPD1.PRO
142 V F P A L G N H D Y W P Q D Q L P I V - - - - - - - T S K V Y S A V A D L W K P MASMPD.PRO

    W L X E E A I S T L R K G G F Y S Q K V X X N P G L R I I S L N T N L Y Y G P N Majority
                      330                 340                 350                 360
178 W L D E E A I S T L R K G G F Y S Q K V T T N P N L R I I S L N T N L Y Y G P N HASM14BP.PRO
158 - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - HASM7AP.PRO
320 W L P A E A L R T L R I G G F Y A - - L S P Y P G L R L I S L N M N F C S R E N HASMSPD1.PRO
175 W L G E E A I S T L K K G G F Y S Q K V A S N P G L R I I S L N T N L Y Y G P N MASMPD.PRO

    I - M T L N K T D P A N Q F E W L E X T L N X S X X N K E K V Y I I A H V P V G Majority
                      370                 380                 390                 400
218 I - M T L N K T D P A N Q F E W L E S T L N N S Q Q N K E K V Y I I A H V P V G HASM14BP.PRO
158 - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - V Y I I A H V P V G HASM7AP.PRO
358 F W L L I N S T D P A G Q L Q W L V G E L Q A A E D R G D K V H I I G H I P P G HASMSPD1.PRO
215 I - M T L N K T D P A N Q F E W L E N T L N S S L W N K E K V Y X I A H V P V G MASMPD.PRO

    Y - L P S S Q N I T A M R E Y Y N E K L I D I F Q K Y S D V I A G Q F Y G H T H Majority
                      410                 420                 430                 440
257 Y - L P S S Q N I T A M R E Y Y N E K L I D I F Q K Y S D V I A G Q F Y G H T H HASM14BP.PRO
168 Y - L P S S Q N I T A M R E Y Y N E K L I D I F Q K Y S D V I A G Q F Y G H T H HASM7AP.PRO
398 H C L K S W S - - - - - W N Y Y R - - - - - I V A R Y E N T L A A Q F F G H T H HASMSPD1.PRO
254 Y - L P Y A T D T P A I R Q Y Y N E K L L D I F R R Y S S V I A G Q F Y G H T H MASMPD.PRO

    R D S I M V L S D K K - - G S P V N S L F V A P A V T P V K G V L E K Q T N N P Majority
                      450                 460                 470                 480
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207 R D S I M V L S D K K - - G S P V N S L F V A P A V T P V K S V L E K Q T N N P HASM7AP.PRO
428 V D E F E V F Y D E E T L S R P L A V A F L A P S A T T Y I G L - - - - - - N P HASMSPD1.PRO
293 R D S L M V L S D X N - - G N P L N S V F V A P A V T P V K G V L Q K E T N N P MASMPD.PRO

    G I R L F Q - - - - Y D P R D Y K L L D M L Q Y Y L N L T E A N L K G E - S I W Majority
                      490                 500                 510                 520
334 G I R L F Q - - - - Y D P R D Y K L L D M L Q Y Y L N L T E A N L K G E - S I W HASM14BP.PRO
245 G I R L F Q - - - - Y D P R D Y K L L D M L Q Y Y L N L T E A N L K G E - S I W HASM7AP.PRO
462 G Y R V Y Q I D G N Y S G S S H V V L D H E T Y I L N L T Q A N I P G A I P H W HASMSPD1.PRO
331 G V R L F Q - - - - Y K P G D Y T L L D M V Q Y Y L N L T E A N L K G E - S N W MASMPD.PRO

    K L E Y I L T Q T Y D I E D L Q P E S L Y G L A K Q F T I L D S K Q F I K Y Y N Majority
                      530                 540                 550                 560
369 K L E Y I L T Q T Y D I E D L Q P E S L Y G L A K Q F T I L D S K Q F I K Y Y N HASM14BP.PRO
280 K L E Y I L T Q T Y D I E D L Q P E S L Y G L A K Q F T I L D S K Q F I K Y Y N HASM7AP.PRO
502 Q L L Y R A R E T Y G L P N T L P T A W H N L V - - Y R M R G D M Q L F Q T F W HASMSPD1.PRO
366 T L E Y V L T Q A Y S V A D L Q P K S L Y A L V Q Q F A T K D S K Q F L K Y Y H MASMPD.PRO
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[redacted]

```
     Y F F V - S Y D S S V T C D K T C K A F Q I C A I M N L D N I S Y A D C - - - - Majority
                    570                 580                 590                 600
409  Y F F V - S Y D S S V T C D K T C K A F Q I C A I M N L D N I S Y A D C - - - - HASM14BP.PRO
320  Y F F V - S Y D S S V T C D K T C K A F Q I C A I M N L D N I S Y A D C - - - - HASM7AP.PRO
540  F L Y H K G H P P S E P C G T P C R L A T L C A Q L S A R A D S P A L C R H L M HASMSPD1.PRO
406  Y Y F V - S Y D S S A T C D Q H C K T L Q V C A I M N L D S M S Y D D C - - - - MASMPD.PRO

     - - - - - - - L K Q L Y I K H N Y -                                          Majority
                    610
444  - - - - - - - L K Q L Y I K H N Y .                                          HASM14BP.PRO
355  - - - - - - - L K Q L Y I K H N Y .                                          HASM7AP.PRO
580  P D G S L P E A Q S L W P R P L F C                                          HASMSPD1.PRO
441  - - - - - - - L K Q - - - - - - H L                                          MASMPD.PRO
```

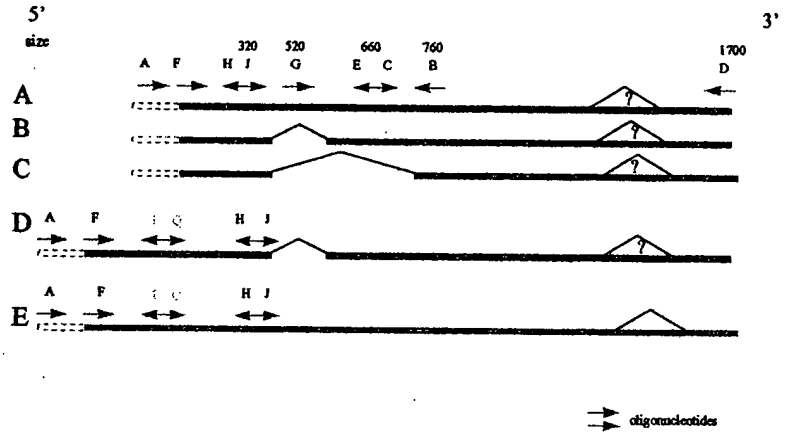
[redacted]

Summary from Evry.

cDNA cloning of the human acid sphingomyelinase-like phosphodiesterase 3a

Background : The overall goal is to construct a transgenic mouse with the human acid sphingomyelinase-like phosphodiesterase 3a gene. In the Genbank databases, the human cDNA is partial but the corresponding mouse cDNA is full length. In view of this data, June Kaplow asked us to provide information on the full length human cDNA.

Status : After a series of electronic elongations on the human ASM-like phosphodiesterase 3a cDNA (Y08136) and experimental validations, 981 bp have been gained on the 5' end. Two EST potential populations in the 5'end have been revealed by the electronic sequence.
The two populations (represented in red and blue) in the 5'end of the sequences have been validated by the wet lab and five transcripts (A, B, C, D and E) have been revealed containing different alternative splices.



The five transcripts A, B, C, D and E have a size of 1686 bp, 1525 bp, 1355 bp, 1739 bp and 1842 bp respectively. They were validated with several oligonucleotides (A, B, C, D, E, F, G, H, J). To find the population containing the « blue splice », it has been necessary to initiate the RT-PCR in the blue sequence as it is a minor population.

No Open Reading Frame was found on the transcripts A, B, C, and D.
The only transcript that possesses an open reading frame (1335 bp) with an ATG as codon +1, is transcript E (1842 bp), which predicts a polypeptide of 445 amino acids length.

The size of the transcript observed by the Northern-blot analysis is approximately 1,8 Kb. A multi-tissues northern-blot shows a better expression on the panceas, kidney and liver. The transcript is less expressed in placenta tissue. We know that the transcript is found in brain tissue, because RT-PCR have been made with RNA brain.

The comparison of the human transcript E sequence with the mouse cDNA of acid sphingomyelinase-like phosphodiesterase 3a shows 79% identity on 1490 nucleotides overlap. The translation comparison of these two sequences shows 80% identity on 448 amino acids overlap.

In conclusion, the trancript E is likely to correspond to the expected human cDNA of acid sphingomyelinase-like phosphodiesterase 3a.

Attachment :

- « SeqTranscripts » : The nucleic sequences of the 5 transcripts A, B, C, D and E.
- « Transcript A -E » : The sequence translation of the 5 transcripts A, B, C, D and E.
- « nucalign » :Nucleic multi-alignments of the 5 transcripts A, B, C, D and E with the mouse Y08135 sequence with the different oligonucleotides.
- « lfastaseqnuc_hom-mouse » : Lfasta : comparison between transcriptE nucleic sequence and mouse nucleic sequence.
- « lfastaprottrE-Mouse » : : Lfasta : comparison between transcriptE sequence translation and mouse sequence translation.

[redacted]he following are the sequences, nucleotide and protein for the novel acid sphingomyelinases for ROI

Human ASMPD3a (14b)

ATGGCGCTGGTGCGCGCACTCGTCTGCTGCCTGCTGACTGCCTGGCACTGCCGCTCCGGCCTCG
GGCTGCCCGTGGCGCCCGCAGGCGGCAGGAATCCTCCTCCGGCGATAGGACAGTTTTGGCATG
TGACTGACTTACACTTAGACCCTACTTACCACATCACAGATGACCACACAAAAGTGTGTGCTT
CATCTAAAGGTGCAAATGCCTCCAACCCTGGCCCTTTTGGAGATGTTCTGTGTGATTCTCCATA
TCAACTTATTTTGTCAGCATTTGATTTTATTAAAAATTCTGGACAAGAAGCATCTTTCATGATA
TGGACAGGGGATAGCCCACCTCATGTTCCTGTACCTGAACTCTCAACAGACACTGTTATAAAT
GTGATCACTAATATGACAACCACCATCCAGAGTCTCTTTCCAAATCTCCAGGTTTTCCCTGCGC
TGGGTAATCATGACTATTGGCCACAGGATCAACTGTCTGTAGTCACCAGTAAAGTGTACAATG
CAGTAGCAAACCTCTGGAAACCATGGCTAGATGAAGAAGCTATTAGTACTTTAAGGAAAGGT
GGTTTTTATTCACAGAAAGTTACAACTAATCCAAACCTTAGGATCATCAGTCTAAACACAAAC
TTGTACTACGGCCCAAATATAATGACACTGAACAAGACTGACCCAGCCAACCAGTTTGAATGG
CTAGAAAGTACATTGAACAACTCTCAGCAGAATAAGGAGAAGGTGTATATCATAGCACATGTT
CCAGTGGGGTATCTGCCATCTTCACAGAACATCACAGCAATGAGAGAATACTATAATGAGAAA
TTGATAGATATTTTTCAAAAATACAGTGATGTCATTGCAGGACAATTTTATGGACACACTCAC
AGAGACAGCATTATGGTTCTTTCAGATAAAAAAGGAAGTCCAGTAAATTCTTTGTTTGTGGCT
CCTGCTGTTACACCAGTGAAGAGTGTTTTAGAAAAAcAGACCAACAATCCTGGTATCAGACTG
TTTCAGTATGATCCTCGTGATTATAAATTATTGGATATGTTGCAGTATTACTTGAATCTGACAG
AGGCGAATCTAAAGGGAGAGTCCATCTGGAAGCTGGAGTATATCCTGACCCAGACCTACGAC
ATTGAAGATTTGCAGCCGGAAAGTTTATATGGATTAGCTAAACAATTTACAATCCTAGACAGT
AAGCAGTTTATAAAATACTACAATTACTTCTTTGTGAGTTATGACAGCAGTGTAACATGTGAT
AAGACATGTAAGGCCTTTCAGATTTGTGCAATTATGAATCTTGATAATATTTCCTATGCAGATT
GCCTCAAACAGCTTTATATAAAGCACAATTACTAG

Human ASMPD3a (7a)

ATGGCGCTGGTGCGCGCACTCGTCTGCTGCCTGCTGACTGCCTGGCACTGCCGCTCCGGCCTCG
GGCTGCCCGTGGCGCCCGCAGGCGGCAGGAATCCTCCTCCGGCGATAGGACAGTTTTGGCATG
TGACTGACTTACACTTAGACCCTACTTACCACATCACAGATGACCACACAAAAGTGTGTGCTT
CATCTAAAGGTGCAAATGCCTCCAACCCTGGCCCTTTTGGAGATGTTCTGTGTGATTCTCCATA
TCAACTTATTTTGTCAGCATTTGATTTTATTAAAAATTCTGGACAAGAAGCATCTTTCATGATA
TGGACAGGGGATAGCCCACCTCATGTTCCTGTACCTGAACTCTCAACAGACACTGTTATAAAT
GTGATCACTAATATGACAACCACCATCCAGAGTCTCTTTCCAAATCTCCAGGTTTTCCCTGCGC
TGGGTAATCATGACTATTGGCCACAGGTGTATATCATAGCACATGTTCCAGTGGGGTATCTGC
CATCTTCACAGAACATCACAGCAATGAGAGAATACTATAATGAGAAATTGATAGATATTTTTC
AAAAGTACAGTGATGTCATTGCAGGACAATTTTATGGACACACTCACAGAGACAGCATTATGG
TTCTTTCAGATAAAAAAGGAAGTCCAGTAAATTCTTTGTTTGTGGCTCCTGCTGTTACACCAGT
GAAGAGTGTTTTAGAAAAACAGACCAACAATCCTGGTATCAGACTGTTTCAGTATGATCCTCG
TGATTATAAATTATTGGATATGTTGCAGTATTACTTGAATCTGACAGAGGCGAATCTAAAGGG
AGAGTCCATCTGGAAGCTGGAGTATATCCTGACCCAGACCTACGACATTGAAGATTTGCAGCC
GGAAAGTTTATATGGATTAGCTAAACAATTTACAATCCTAGACAGTAAGCAGTTTATAAAATA
CTACAATTACTTCTTTGTGAGTTATGACAGCAGTGTAACATGTGATAAGACATGTAAGGCCTTT
CAGATTTGTGCAATTATGAATCTTGATAATATTTCCTATGCAGATTGCCTCAAACAGCTTTATA
TAAAGCACAATTACTAG

Human ASMPD3a (14b)

MALVRALVCCLLTAWHCRSGLGLPVAPAGGRNPPPAIGQFWHVTDLHLDPTYHITDDHTKVCASS
KGANASNPGPFGDVLCDSPYQLILSAFDFIKNSGQEASFMIWTGDSPPHVPVPELSTDTVINVITNM
TTTIQSLFPNLQVFPALGNHDYWPQDQLSVVTSKVYNAVANLWKPWLDEEAISTLRKGGFYSQKV
TTNPNLRIISLNTNLYYGPNIMTLNKTDPANQFEWLESTLNNSQQNKEKVYIIAHVPVGYLPSSQNI
TAMREYYNEKLIDIFQKYSDVIAGQFYGHTHRDSIMVLSDKKGSPVNSLFVAPAVTPVKSVLEKQT

NNPGIRLFQYDPRDYKLLDMLQYYLNLTEANLKGESIWKLEYILTQTYDIEDLQPESLYGLAKQFTI
LDSKQFIKYYNYFFVSYDSSVTCDKTCKAFQICAIMNLDNISYADCLKQLYIKHNY.

Human ASMPD3a (7b)
MALVRALVCCLLTAWHCRSGLGLPVAPAGGRNPPPAIGQFWHVTDLHLDPTYHITDDHTKVCASS
KGANASNPGPFGDVLCDSPYQLILSAFDFIKNSGQEASFMIWTGDSPPHVPVPELSTDTVINVITNM
TTTIQSLFPNLQVFPALGNHDYWPQVYIIAHVPVGYLPSSQNITAMREYYNEKLIDIFQKYSDVIAG
QFYGHTHRDSIMVLSDKKGSPVNSLFVAPAVTPVKSVLEKQTNNPGIRLFQYDPRDYKLLDMLQY
YLNLTEANLKGESIWKLEYILTQTYDIEDLQPESLYGLAKQFTILDSKQFIKYYNYFFVSYDSSVTC
DKTCKAFQICAIMNLDNISYADCLKQLYIKHNY.

Transcript E

MAP of: CV08136Eder.txt check: 7471 from: 1 to: 1842

```
      TGACTCGCTGCGGAATCTGCCTTTGCACGTGATCAGTCGGACGTCTACACCCGCAGCCGT
    1 ---------+---------+---------+---------+---------+---------+ 60
      ACTGAGCGACGCCTTAGACGGAAACGTGCACTAGTCAGCCTGCAGATGTGGGCGTCGGCA

a       * L A A E S A F A R D Q S D V Y T R S R  -
b        D S L R N L P L H V I S R T S T P A A V -
c         T R C G I C L C T * S V G R L H P Q P S -
    1 ---------+---------+---------+---------+---------+---------+ 60
d          S E S R F R G K C T I L R V D V G A A T -
e           S A A S D A K A R S * D S T * V R L R -
f            V R Q P I Q R Q V H D T P R R C G C G  -

      CTTCTGTCTCCGCCTCACCCTCAGGCCTGACGGTCCGAGTGGAGCTGCGGGACAGCCCGA
   61 ---------+---------+---------+---------+---------+---------+ 120
      GAAGACAGAGGCGGAGTGGGAGTCCGGACTGCCAGGCTCACCTCGACGCCCTGTCGGGCT

a       L L S P P H P Q A * R S E W S C G T A R  -
b        F C L R L T L R P D G P S G A A G Q P E -
c         S V S A S P S G L T V R V E L R D S P N -
   61 ---------+---------+---------+---------+---------+---------+ 120
d          K Q R R R V R L G S P G L P A A P C G S -
e           R R D G G * G * A Q R D S H L Q P V A R -
f            D E T E A E G E P R V T R T S S R S L G  -

      ACCTCCAGGTCAGCCCCGCGGCCCTCCATGGCGCTGGTGCGCGCACTCGTCTGCTGCCTG
  121 ---------+---------+---------+---------+---------+---------+ 180
      TGGAGGTCCAGTCGGGGCGCCGGGAGGTACCGCGACCACGCGCGTGAGCAGACGACGGAC

a       T S R S A P R P S M A L V R A L V C C L  -
b        P P G Q P R G P P W R W C A H S S A A C -
c         L Q V S P A A L H G A G A R T R L L P A -
  121 ---------+---------+---------+---------+---------+---------+ 180
d          G G P * G R P G G H R Q H A C E D A A Q -
e           V E L D A G R G E M A S T R A S T Q Q R -
f            F R W T L G A A R W P A P A R V R R S G  -

      CTGACTGCCTGGCACTGCCGCTCCGGCCTCGGGCTGCCCGTGGCGCCCGCAGGCGGCAGG
  181 ---------+---------+---------+---------+---------+---------+ 240
      GACTGACGGACCGTGACGGCGAGGCCGGAGCCCGACGGGCACCGCGGGCGTCCGCCGTCC

a       L T A W H C R S G L G L P V A P A G G R  -
b        * L P G T A A P A S G C P W R P Q A A G -
c         D C L A L P L R P R A A R G A R R R Q E -
  181 ---------+---------+---------+---------+---------+---------+ 240
d          Q S G P V A A G A E P Q G H R G C A A P -
e           S V A Q C Q R E P R P S G T A G A P P L -
f            A S Q R A S G S R G R A A R P A R L R C  -

      AATCCTCCTCCGGCGATAGGACAGTTTTGGCATGTGACTGACTTACACTTACACTTAGAC
  241 ---------+---------+---------+---------+---------+---------+ 300
      TTAGGAGGAGGCCGCTATCCTGTCAAAACCGTACACTGACTGAATGTGAATGTGAATCTG

a       N P P P A I G Q F W H V T D L H L H L D  -
b        I L L R R * D S F G M * L T Y T Y T * T -
c         S S S G D R T V L A C D * L T L T L R P -
  241 ---------+---------+---------+---------+---------+---------+ 300
d          I R R R R Y S L K P M H S V * V * V * V -
e           F G G G A I P C N Q C T V S K C K C K S -
f            S D E E P S L V T K A H S Q S V S V S L  -

      CCTACTTACCACATCACAGATGACCACACAAAAGTGTGTGCTTCATCTAAAGGTGCAAAT
  301 ---------+---------+---------+---------+---------+---------+ 360
      GGATGAATGGTGTAGTGTCTACTGGTGTGTTTTCACACACGAAGTAGATTTCCACGTTTA

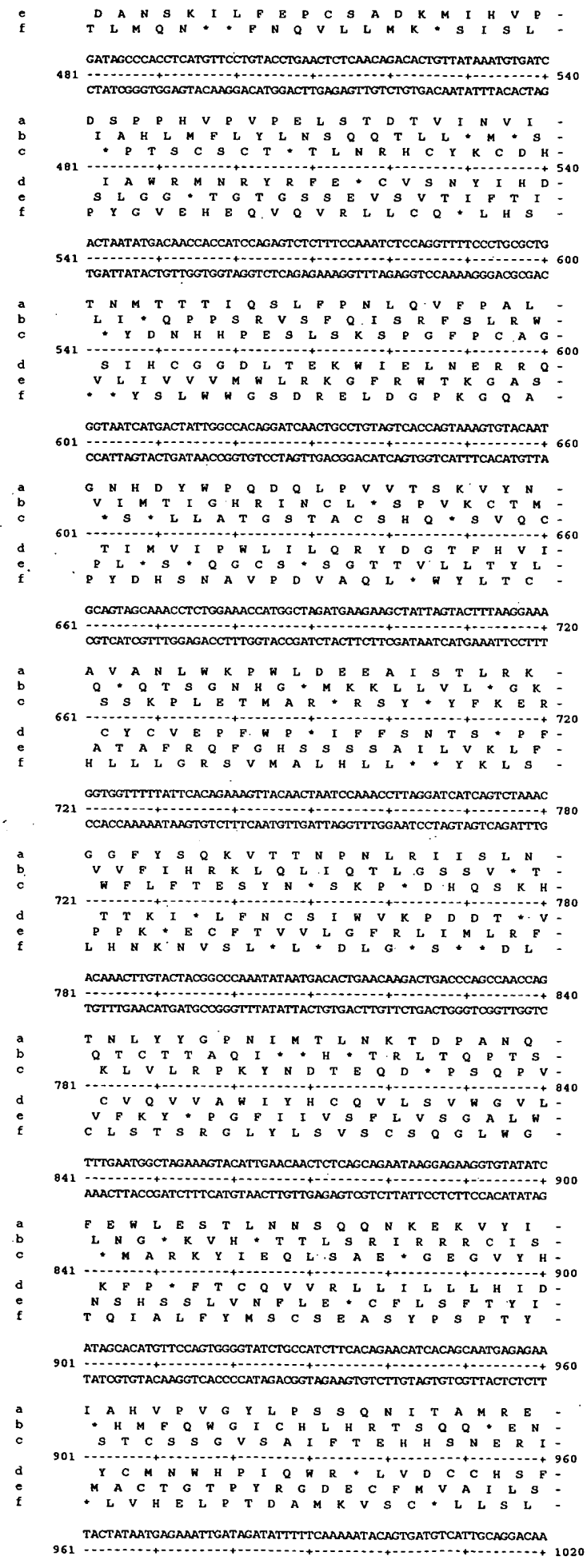
a       P T Y H I T D D H T K V C A S S K G A N  -
b        L L T T S Q M T T Q K C V L H L K V Q M -
c         Y L P H H R * P H K S V C F I * R C K C -
  301 ---------+---------+---------+---------+---------+---------+ 360
d          R S V V D C I V V C F H T S * R F T C I -
e           G V * W M V S S W V F T H A E D L P A F -
f            G * K G C * L H G C L L T H K M * L H L  -

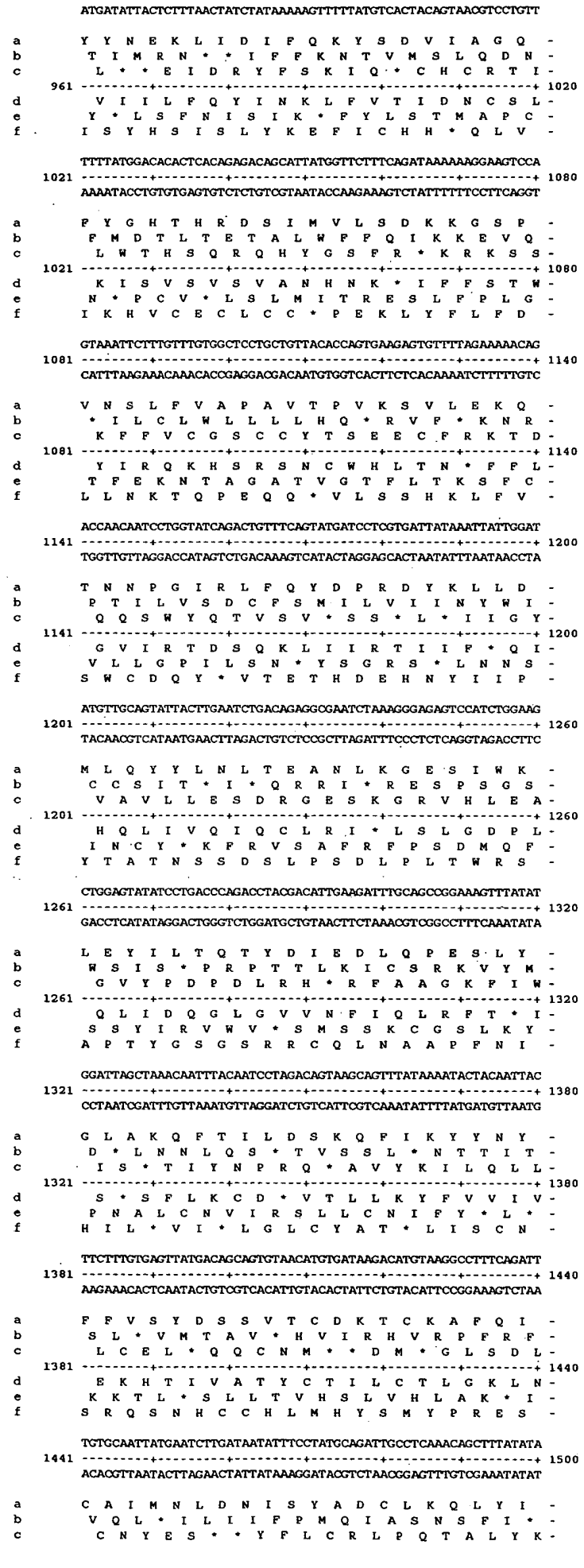
      GCCTCCAACCCTGGCCCTTTTGGAGATGTTCTGTGTGATTCTCCATATCAACTTATTTTG
  361 ---------+---------+---------+---------+---------+---------+ 420
      CGGAGGTTGGGACCGGGAAAACCTCTACAAGACACACTAAGAGGTATAGTTGAATAAAAC

a       A S N P G P F G D V L C D S P Y Q L I L  -
b        P P T L A L L E M F C V I L H I N L F C -
c         L Q P W P F W R C S V * F S I S T Y F V -
  361 ---------+---------+---------+---------+---------+---------+ 420
d          G G V R A R K S I N Q T I R W I L K N Q -
e           A E L G P G K P S T R H S E G Y * S I K -
f            H R W G Q G K Q L H E T H N E M D V * K  -

      TCAGCATTTGATTTTATTAAAAATTCTGGACAAGAAGCATCTTTCATGATATGGACAGGG
  421 ---------+---------+---------+---------+---------+---------+ 480
      AGTCGTAAACTAAAATAATTTTTAAGACCTGTTCTTCGTAGAAAGTACTATACCTGTCCC

a       S A F D F I K N S G Q E A S F M I W T G  -
b        Q H L I L L K I L D K K H L S * Y G Q G -
c         S I * F Y * K F W T R S I F H D M D R G -
  421 ---------+---------+---------+---------+---------+---------+ 480
d          * C K I K N F I R S L F C R E H Y P C P -
```


e D A N S K I L F E P C S A D K M I H V P -
f T L M Q N * * F N Q V L L M K * S I S L -
GATAGCCCACCTCATGTTCCTGTACCTGAACTCTCAACAGACACTGTTATAAATGTGATC
481 540
CTATCGGGTGGAGTACAAGGACATGGACTTGAGAGTTGTCTGTGACAATATTTACACTAG
a D S P P H V P V P E L S T D T V I N V I -
b I A H L M F L Y L N S Q Q T L L * M * S -
c * P T S C S C T * T L N R H C Y K C D H -
481 540
d I A W R M N R Y R F E * C V S N Y I H D -
e S L G G * T G T G S S E V S V T I F T I -
f P Y G V E H E Q V Q V R L L C Q * L H S -
ACTAATATGACAACCACCATCCAGAGTCTCTTTCCAAATCTCCAGGTTTTCCCTGCGCTG
541 600
TGATTATACTGTTGGTGGTAGGTCTCAGAGAAAGGTTTAGAGGTCCAAAAGGGACGCGAC
a T N M T T T I Q S L F P N L Q V F P A L -
b L I * Q P P S R V S F Q I S R F S L R W -
c * Y D N H H P E S L S K S P G F P C A G -
541 600
d S I H C G G D L T E K W I E L N E R R Q -
e V L I V V V M W L R K G F R W T K G A S -
f * * Y S L W W G S D R E L D G P K G Q A -
GGTAATCATGACTATTGGCCACAGGATCAACTGCCTGTAGTCACCAGTAAAGTGTACAAT
601 660
CCATTAGTACTGATAACCGGTGTCCTAGTTGACGGACATCAGTGGTCATTTCACATGTTA
a G N H D Y W P Q D Q L P V V T S K V Y N -
b V I M T I G H R I N C L * S P V K C T M -
c * S * L L A T G S T A C S H Q * S V Q C -
601 660
d T I M V I P W L I L Q R Y D G T F H V I -
e P L * S * Q G C S * S G T T V L L T Y L -
f P Y D H S N A V P D V A Q L * W Y L T C -
GCAGTAGCAAACCTCTGGAAACCATGGCTAGATGAAGAAGCTATTAGTACTTTAAGGAAA
661 720
CGTCATCGTTTGGAGACCTTTGGTACCGATCTACTTCTTCGATAATCATGAAATTCCTTT
a A V A N L W K P W L D E E A I S T L R K -
b Q * Q T S G N H G * M K K L L V L * G K -
c S S K P L E T M A R * R S Y * Y F K E R -
661 720
d C Y C V E P F W P * I F F S N T S * P F -
e A T A F R Q F G H S S S S A I L V K L F -
f H L L L G R S V M A L H L L * * Y K L S -
GGTGGTTTTTATTCACAGAAAGTTACAACTAATCCAAACCTTAGGATCATCAGTCTAAAC
721 780
CCACCAAAAATAAGTGTCTTTCAATGTTGATTAGGTTTGGAATCCTAGTAGTCAGATTTG
a G G F Y S Q K V T T N P N L R I I S L N -
b V V F I H R K L Q L I Q T L G S S V * T -
c W F L F T E S Y N * S K P * D H Q S K H -
721 780
d T T K I * L F N C S I W V K P D D T * V -
e P P K * E C F T V V L G F R L I M L R F -
f L H N K N V S L * L * D L G * S * * D L -
ACAAACTTGTACTACGGCCCAAATATAATGACACTGAACAAGACTGACCCAGCCAACCAG
781 840
TGTTTGAACATGATGCCGGGTTTATATTACTGTGACTTGTTCTGACTGGGTCGGTTGGTC
a T N L Y Y G P N I M T L N K T D P A N Q -
b Q T C T T A Q I * * H * T R L T Q P T S -
c K L V L R P K Y N D T E Q D * P S Q P V -
781 840
d C V Q V V A W I Y H C Q V L S V W G V L -
e V F K Y * P G F I I V S F L V S G A L W -
f C L S T S R G L Y L S V S C S Q G L W G -
TTTGAATGGCTAGAAAGTACATTGAACAACTCTCAGCAGAATAAGGAGAAGGTGTATATC
841 900
AAACTTACCGATCTTTCATGTAACTTGTTGAGAGTCGTCTTATTCCTCTTCCACATATAG
a F E W L E S T L N N S Q Q N K E K V Y I -
b L N G * K V H * T T L S R I R R R C I S -
c * M A R K Y I E Q L S A E * G E G V Y H -
841 900
d K F P * F T C Q V V R L L I L L L H I D -
e N S H S S L V N F L E * C F L S F T Y I -
f T Q I A L F Y M S C S E A S Y P S P T Y -
ATAGCACATGTTCCAGTGGGGTATCTGCCATCTTCACAGAACATCACAGCAATGAGAGAA
901 960
TATCGTGTACAAGGTCACCCCATAGACGGTAGAAGTGTCTTGTAGTGTCGTTACTCTCTT
a I A H V P V G Y L P S S Q N I T A M R E -
b * H M F Q W G I C H L H R T S Q Q * E N -
c S T C S S G V S A I F T E H H S N E R I -
901 960
d Y C M N W H P I Q W R * L V D C C H S F -
e M A C T G T P Y R G D E C F M V A I L S -
f * L V H E L P T D A M K V S C * L L S L -
TACTATAATGAGAAATTGATAGATATTTTTCAAAAATACAGTGATGTCATTGCAGGACAA
961 1020



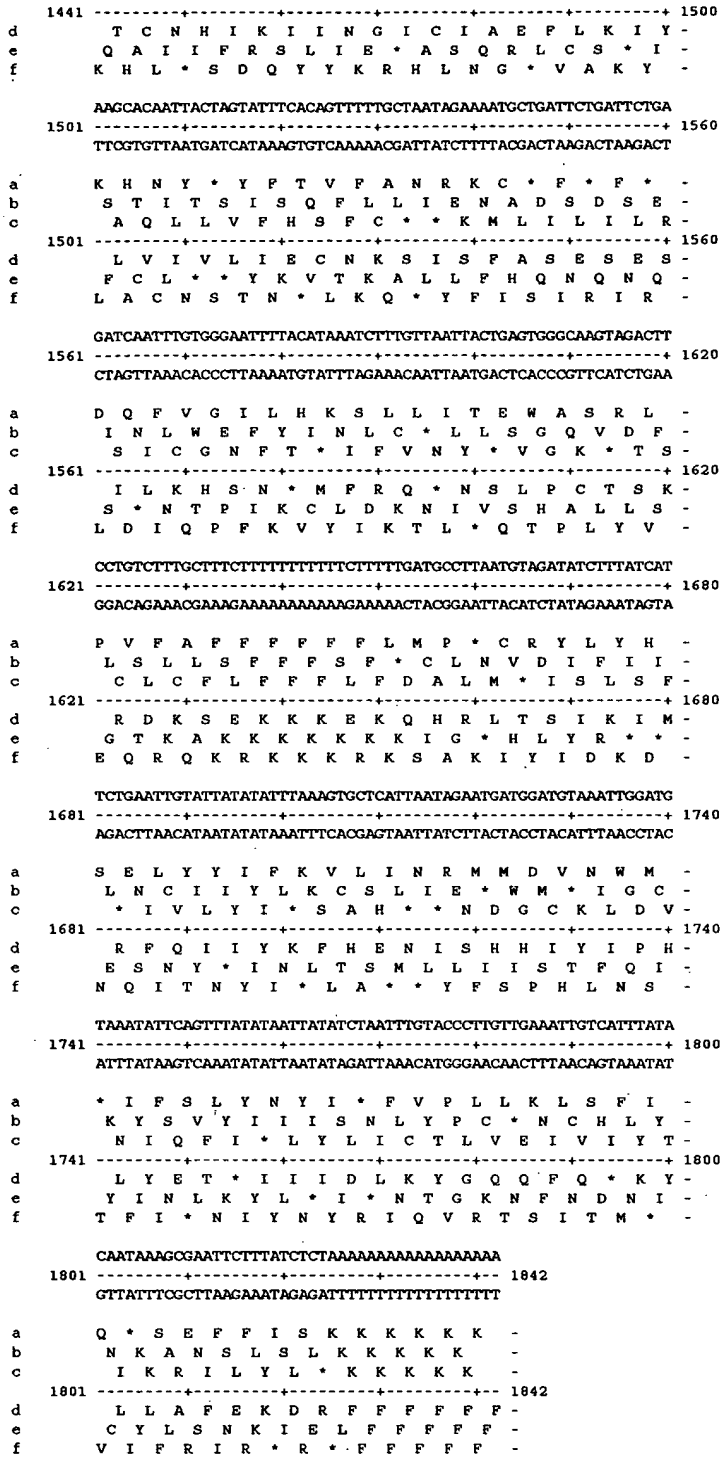


Exhibit B

Comparison of NFIF 14b (SEQ ID NO:3) with Nucleotide Sequence Disclosed in Sugano et al.

```
14b:    1 atggcgctggtgcgcgcactcgtctgctgcctgctgactgcctggcactgccgctccggc 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.:  72 atggcgctggtgcgcgcactcgtctgctgcctgctgactgcctggcactgccgctccggc 131

14b:   61 ctcgggctgcccgtggcgcccgcaggcggcaggaatcctcctccggcgataggacagttt 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 132 ctcgggctgcccgtggcgcccgcaggcggcaggaatcctcctccggcgataggacagttt 191

14b: 121 tggcatgtgactgacttacacttagaccctacttaccacatcacagatgaccacacaaaa 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 192 tggcatgtgactgacttacacttagaccctacttaccacatcacagatgaccacacaaaa 251

14b: 181 gtgtgtgcttcatctaaaggtgcaaatgcctccaaccctggccctttttggagatgttctg 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 252 gtgtgtgcttcatctaaaggtgcaaatgcctccaaccctggccctttttggagatgttctg 311

14b: 241 tgtgattctccatatcaacttattttgtcagcatttgattttattaaaaattctggacaa 300
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 312 tgtgattctccatatcaacttattttgtcagcatttgattttattaaaaattctggacaa 371

14b: 301 gaagcatctttcatgatatggacaggggatagcccacctcatgttcctgtacctgaactc 360
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 372 gaagcatctttcatgatatggacaggggatagcccacctcatgttcctgtacctgaactc 431

14b: 361 tcaacagacactgttataaatgtgatcactaatatgacaaccaccatccagagtctcttt 420
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 432 tcaacagacactgttataaatgtgatcactaatatgacaaccaccatccagagtctcttt 491

14b: 421 ccaaatctccaggttttccctgcgctgggtaatcatgactattggccacaggatcaactg 480
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 492 ccaaatctccaggttttccctgcgctgggtaatcatgactattggccacaggatcaactg 551

14b: 481 tctgtagtcaccagtaaagtgtacaatgcagtagcaaacctctggaaaccatggctagat 540
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 552 cctgtagtcaccagtaaagtgtacaatgcagtagcaaacctctggaaaccatggctagat 611

14b: 541 gaagaagctattagtactttaaggaaaggtggtttttattcacagaaagttacaactaat 600
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 612 gaagaagctattagtactttaaggaaaggtggtttttattcacagaaagttacaactaat 671

14b: 601 ccaaaccttaggatcatcagtctaaacacaaacttgtactacggcccaaatataatgaca 660
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 672 ccaaaccttaggatcatcagtctaaacacaaacttgtactacggcccaaatataatgaca 731

14b: 661 ctgaacaagactgacccagccaaccagtttgaatggctagaaagtacattgaacaactct 720
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 732 ctgaacaagactgacccagccaaccagtttgaatggctagaaagtacattgaacaactct 791
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```
 14b:  721 cagcagaataaggagaaggtgtatatcatagcacatgttccagtggggtatctgccatct  780
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.:  792 cagcagaataaggagaaggtgtatatcatagcacatgttccagtggggtatctgccatct  851

 14b:  781 tcacagaacatcacagcaatgagagaatactataatgagaaattgatagatatttttcaa  840
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.:  852 tcacagaacatcacagcaatgagagaatactataatgagaaattgatagatatttttcaa  911


 14b:  841 aaatacagtgatgtcattgcaggacaattttatggacacactcacagagacagcattatg  900
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.:  912 aaatacagtgatgtcattgcaggacaattttatggacacactcacagagacagcattatg  971

 14b:  901 gttctttcagataaaaaaggaagtccagtaaattctttgtttgtggctcctgctgttaca  960
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.:  972 gttctttcagataaaaaaggaagtccagtaaattctttgtttgtggctcctgctgttaca 1031

 14b:  961 ccagtgaagagtgttttagaaaaacagaccaacaatcctggtatcagactgtttcagtat 1020
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 1032 ccagtgaagagtgttttagaaaaacagaccaacaatcctggtatcagactgtttcagtat 1091

 14b: 1021 gatcctcgtgattataaattattggatatgttgcagtattacttgaatctgacagaggcg 1080
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 1092 gatcctcgtgattataaattattggatatgttgcagtattacttgaatctgacagaggcg 1151

 14b: 1081 aatctaaagggagagtccatctggaagctggagtatatcctgacccagacctacgacatt 1140
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 1152 aatctaaagggagagtccatctggaagctggagtatatcctgacccagacctacgacatt 1211

 14b: 1141 gaagatttgcagccggaaagtttatatggattagctaaacaatttacaatcctagacagt 1200
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 1212 gaagatttgcagccggaaagtttatatggattagctaaacaatttacaatcctagacagt 1271

 14b: 1201 aagcagtttataaaatactacaattacttctttgtgagttatgacagcagtgtaacatgt 1260
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 1272 aagcagtttataaaatactacaattacttctttgtgagttatgacagcagtgtaacatgt 1331

 14b: 1261 gataagacatgtaaggcctttcagatttgtgcaattatgaatcttgataatatttcctat 1320
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sug.: 1332 gataagacatgtaaggcctttcagatttgtgcaattatgaatcttgataatatttcctat 1391

 14b: 1321 gcagattgcctcaaacagctttatataaagcacaattactag 1362
           |||||||||||||||||||||||||||||||||||||||
Sug.: 1392 gcagattgcctcaaacagctttatataaagcacaattactag 1433
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